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Electrical status epilepticus during sleep: A study of 22 patients

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Abstract

Objective: The aim of this study was to evaluate the clinical and imaging characteristics, treatment results, and prognosis of patients with electrical status epilepticus during sleep (ESES). *Method:* A total of 22 patients with ESES pattern on EEG were retrospectively studied. *Results:* The first neurological symptoms were seen at a mean age of 4.4 years. The first symptoms in 77% of the patients were seizures. Other symptoms were hyperactivity, restlessness, insomnia, disinhibition, autistic behavior, speech retardation and deterioration in school performance. Diagnosis of ESES was made at a mean age of 7.45 years, approximately 3 years after the first symptom. Magnetic resonance imaging (MRI) was abnormal in 36% of the patients. Single photon emission computed tomography (SPECT) showed focal hypoperfusion after resolution of ESES involving left temporoparietal and right posterior temporal areas in four patients including three with normal MRI, and one with periventricular leukomalacia without focal cortical lesion. First line treatment with valproic acid monotherapy was not effective. Electrical status epilepticus during sleep disappeared in 82% of the patients on clobazam and 70% of the patients on clonazepam in combination with valproic acid within a few months. Topiramate was not found to be effective. A significant decrease in intelligence quotient (IQ) scores was found in 66% of the patients compared to the baseline. *Conclusions:* ESES should be considered in children with new onset behavioral, cognitive, and speech problems with or without seizures. The high frequency of focal seizures and focal findings on SPECT suggest a focal origin. Clonazepam and clobazam were most effective in our cohort.

Keywords: Electrical status epilepticus during sleep; Continuous spikes and waves during slow wave sleep; Epileptic encephalopathy

1. Introduction

Electrical status epilepticus during sleep or ESES, is a term that describes an EEG pattern where epileptiform discharges show a significant increase during sleep associated with representative clinical signs [1]. It is seen in epileptic syndromes such as atypical rolandic epilepsy, acquired opercular syndrome, Landau–Kleffner syndrome (LKS), and continuous spikes and waves during slow wave sleep (CSWS) [2]. Although CSWS and ESES are used interchangeably in the literature, some authors prefer ESES to describe the electrographic pattern and CSWS to describe the clinical syndrome [1,3–6]. This distinction appears appropriate to prevent terminological confusion of the EEG pattern (i.e. ESES) seen in LKS, with the epileptic encephalopathy seen with global regression in cognitive functions (i.e. CSWS).

Electrical status epilepticus during sleep shows almost near-continuous spike-waves discharges with marked activation in slow sleep that are generally diffuse and bilateral at a frequency of 1.5–3 Hz and is associated with various types of seizures together with

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neuropsychological regression. Although spike-waves activities are suggested to occur during at least 85% of non-REM sleep in the classic definition, lower threshold values have been accepted in subsequent studies if together with an appropriate clinical picture [2,5]. It is considered to be age related and self-limited with an uncertain etiology, and although rare it is probably underrecognized [1,7]. Continuous spikes and waves in slow-wave sleep and LKS are epileptic encephalopathies of childhood that have many common features and pathophysiological mechanisms [8]. It has been hypothesized that frequent interictal epileptiform discharges developing in the critical period may strengthen the synaptic contacts that are supposed to disappear in the normal developing brain, and may eventually cause deterioration of the functions in a given region [8]. It still remains unknown if interictal discharges are the direct cause of developmental deterioration or the epiphenomenon mirroring the underlying brain pathology. Much of the evidence is needed to declare the causal relationship between 'EEG findings' and abnormal development [9]. Executive functions, and memory loss, neuropsychiatric symptoms in the form of autistic-like or psychotic behaviors and more global regression are seen together with epileptiform activities affecting the frontal region in CSWS while there is a paroxysmal disorder that develops from the posterior temporal area and causes auditory agnosia and language deficits in LKS [10].

The purpose of the study was to examine the clinical picture, imaging characteristics, and psychometric assessment of patients with an ESES pattern on EEG and their responses to treatment.

2. Patients and methods

The study was approved by Hacettepe University Medical Faculty Department of Pediatrics Board. Medical records of twenty two consecutive patients with ESES pattern on EEG followed at the department of pediatric neurology between April 2000 and April 2002 were studied retrospectively. Inclusion criteria were as follows [11,12]: (1) Seizures with focal or apparently generalized onset (atypical absences, myoclonic, atonic or generalized seizures, focal motor, complex-partial); (2) global or selective cognitive or language regression and/or behavioral disturbances connected to the ESES period; (3) motor impairments (such as ataxia, dyspraxia, dystonia or unilateral motor deficits) related to the ESES period and (4) typical EEG findings characterized by spike wave discharges occupying more than 85% of non-REM sleep. The patients with CSWS, LKS, and rolandic epilepsy who had the criteria were included in the study. The spike-wave index was visually counted based on the total number of the spike-waves per second. All patients underwent a clinical evaluation including history, physical and neurological examinations, sleep and awake EEGs, psychometric tests and brain MRI results. Single photon emission computed tomography was available in 12 patients. SPECT was performed after obtaining verbal consent. Patients with an underlying etiology were classified as symptomatic while others were classified as cryptogenic. Follow up EEGs under different treatment regimens were evaluated along with neuropsychological data. Cognitive functions of the patients were evaluated with the WISC-R test, or the Stanford–Binet scale when the WISC-R test could not be administered.

The Wilcoxon test was utilized to determine the significance of the difference between the first and last total IQs, first and last verbal IQs, and first and last performance IQs.

3. Results

3.1. Clinical characteristics

Clinical characteristics of the patients were shown in Table 1. There was a total of 22 patients (16 males, 6 females). Parents were relatives in seven patients. Seven patients (32%) had a family history of epilepsy. Ten patients (45.4%) were classified as symptomatic and three as idiopathic partial epilepsy of childhood (all of them had rolandic epilepsy), and 9 as cryptogenic. Eight patients had perinatal insult (4 perinatal asphyxia, two intrauterine infection, that one of them had bilateral polymicrogyria associated with intrauterine cytomegalovirus infection, one meconium aspiration and neonatal hypoglycemia, one neonatal hypoglycemia). One patient had an arachnoid cyst and one had mental retardation in the symptomatic group.

The first neurological symptoms of the patients had emerged at a mean age of 4.4 years (10 months–13 years). The diagnosis of ESES on EEG was made at an average of 3 years (0–13.5 years) after the initial neurological symptom. Onset of ESES was at a mean age of 7.45 years (2 years 10 months–17 years). The mean ESES duration was 22.4 months.

In 17 patients (77%) the first neurological symptom was seizures. Three patients (13%) presented with problems such as hyperactivity, restlessness, insomnia, behavioral problems at school and autistic behavior, one had delayed speech (4.5%), one had deterioration in school performance (4.5%). All patients had seizures except one (patient 3). While two of them had merely seizures (patients 4 and 22), the rest of the patients had learning, behavior, or attention problems at varying degrees. According to syndromic classification, one patient was diagnosed with Landau–Kleffner syndrome. The other three patients had rolandic epilepsy, and the remaining 18 patients were classified as CSWS.

Table 1
Clinical characteristics of the patients.

Patient	Gender	Age at first symptom (year/month)	Age at onset of ESES (year/month)	First symptom	Other symptoms	Etiological factors	Seizure type	Consanguinity	Family history of epilepsy	Epileptic syndrome
1	M	5 y 6 m	6 y 6 m	Convulsion	Hyperactivity, attention deficit	Neonatal hypoglycemia	– Complex partial	∅	+	CSWS
2	M	9 y	10 y 6 m	Deterioration in school performance	Convulsion, agitation, distractibility, language regression	Birth asphyxia	– Complex partial – Atypical absences	∅	∅	CSWS
3	M	3 y	6 y 6 m	Delayed speech	Behavioral problems, aggressiveness, restlessness, mental retardation	–	–	∅	∅	LKS
4	F	1 y 11 m	2 y 10 m	Convulsion	–	–	– Atonic	+I°	∅	CSWS
5	F	2 y	2 y 10 m	Convulsion	Attention deficit, language regression	–	– Atonic, – Complex partial	+3°	∅	CSWS
6	M	6 y 6 m	7 y 6 m	Behavioral problems, disinhibition	Language regression, school failure, convulsions, hyperactivity, attention deficit	–	– Simple partial – Complex partial	∅	∅	CSWS
7	M	1 y 6 m	3 y 8 m	Autistic like behavior	Convulsions, hyperactivity	–	– Atonic – Simple partial – Atypical absences	∅	∅	CSWS
8	F	6 y	7 y 3 m	Convulsion	Deterioration in school performance, attention deficit, aggressiveness	–	– Complex partial	∅	∅	BRE
9	M	13 y	17 y	Convulsion	Mental retardation, impulsivity, attention deficit	Mental retardation	– Generalized	+I°	+	CSWS
10	F	3 y 6 m	7 y	Convulsion	Mental retardation	–	– Complex partial – Atonic	+I°	+	CSWS
11	M	4 y	4 y 4 m	Convulsion	Hyperactivity, attention deficit, impulsivity	Meconium aspiration + Neonatal hypoglycemia	– Complex partial – Secondary generalized	∅	+	CSWS

Table 1 (*continued*)

Patient	Gender	Age at first symptom (year/month)	Age at onset of ESES (year/month)	First symptom	Other symptoms	Etiological factors	Seizure type	Consanguinity	Family history of epilepsy	Epileptic syndrome
12	M	1 y 6 m	15 y	Convulsion	Mental retardation, language regression	Microcephaly, small for gestational age, sequelae of intrauterine infection	– Complex partial – Simple partial – Atonic – Atypical absences	+I°	∅	CSWS
13	M	6 y 5 m	7 y	Convulsion	School failure	Arachnoid cyst	– Simple partial – Secondary generalized	∅	+	CSWS
14	M	6 y 9 m	6 y 9 m	Convulsion	Deterioration in school performance, aggressiveness, hyperactivity, attention deficit	–	– Complex partial	∅	∅	CSWS
15	M	1 y 6 m	4 y	Convulsion	Hyperactivity, attention deficit, language regression, mental deterioration	Birth asphyxia	– Secondary generalized – Complex partial – Simple partial	∅	+	CSWS
16	F	3 y	4 y	Convulsion	Mental deterioration, hyperactivity, attention deficit	Birth asphyxia, mental retardation	– Complex partial	∅	∅	CSWS
17	M	1 y 2 m	8 y	Convulsion	Severe mental retardation	Birth asphyxia, severe mental retardation	– Complex partial – Secondary generalized	∅	∅	CSWS
18	M	10 m	8 y	Restlessness, hyperactivity, sleeplessness	Attention deficit, distractibility, convulsions	–	– Generalized	∅	∅	CSWS
19	F	5 y	11 y	Convulsion	Language regression	Mental retardation, sequelae of intrauterine CMV infection, cortical dysplasia	– Complex partial – Simple partial – Atypical absences	+I°		CSWS
20	M	5 y	7 y 5 m	Convulsion	Mental deterioration, language regression, attention deficit, impulsivity	–	– Atonic – Generalized – Myoclonic	∅	+	CSWS

(*continued on next page*)

Table 1 (*continued*)

Patient	Gender	Age at first symptom (year/month)	Age at onset of ESES (year/month)	First symptom	Other symptoms	Etiological factors	Seizure type	Consanguinity	Family history of epilepsy	Epileptic syndrome
21	M	4 y	7 y	Convulsion	Mental deterioration	–	– Atypical absences – Simple partial – Complex partial – Atonic – Myoclonic – Secondary generalized	+I°	∅	BRE
22	M	8 y	12 y	Convulsion	–	–	– Simple partial – Complex partial	∅	∅	BRE

3.2. Seizures

Seizures were seen in all patients (95.4%) except one. The most commonly seen seizure types were simple or complex partial seizures. Seventeen patients (77%) had partial seizures alone or accompanied by other seizure types such as atonic, atypical absence, generalized tonic–clonic seizures. The frequency of partial seizures ranged 3–4 times per year to 10–15 times a day. Secondary generalized tonic–clonic seizures were seen in 5 patients (23%).

The second most common type of seizure was atonic seizures. Seven patients (32%) had atonic seizures alone or together with other seizure types. The frequency of atonic seizures ranged between 5–6 and 100–200 times per day. Atypical absence seizures were seen in five patients (22.7%), generalized tonic–clonic seizures in three patients, and myoclonic seizures in two patients (9%).

3.3. EEG findings

The baseline activity during the awake state was normal in 10 of 12 patients (83.4%) in the cryptogenic and idiopathic groups, and 4 of 10 patients (40%) in the symptomatic group (Table 2). Epileptiform activity was present in all awake EEGs (21/22) except for one. Sleep EEGs following recovery of ESES revealed unifocal or multifocal epileptiform discharges with or without secondary bilateral synchrony. EEG samples are shown in Fig. 1a–d.

3.4. Imaging findings

Magnetic resonance imaging was performed for all patients and 8/22 were abnormal (Table 2). Abnormal findings included cerebellar atrophy in two patients, periventricular leukomalacia in two patients, and mild left hippocampal atrophy, right frontoparietal and left parietal polymicrogyria, arachnoid cyst, and mild cortical atrophy each in one patient (Fig. 2).

Single photon emission computed tomography was available in 12 patients, five during ESES and seven after the resolution of ESES. Five of 12 patients showed hypoperfusion on SPECT (Fig. 3). One patient showed right frontal hypoperfusion due to an arachnoid cyst during ESES. Four patients showed hypoperfusion after resolution of ESES involving on the left temporal or temporoparietal and right posterior temporal area. Hypoperfusion only was found in four patients who underwent SPECT after the resolution of ESES.

Magnetic resonance imaging was normal in three of four patients with hypoperfusion on SPECT (patients 2, 7 and 14). MRI showed periventricular leukomalacia and cortical atrophy, without focal cortical lesions in patient 12 with hypoperfusion on SPECT.

3.5. Treatment

Treatment of the patients was shown in Table 3. Patients were on valproic acid (VPA) (13 patients), carbamazepine (seven patients), phenobarbital (five

Table 2
Neuroimaging and EEG findings.

	Etiology	MRI	SPECT	EEG background	EEG during ESES		EEG during remission	
					Wakefulness epileptiform activity	Sleep	Wakefulness epileptiform activity	Sleep epileptiform activity
1	Symptomatic	Periventricular leukomalacia	–	N	Left parietooccipital	ESES	Right frontal	Secondary generalized
2	Symptomatic	N	Hypoperfusion in left parietotemporal	N	Generalized	ESES	Left frontal	Activated with sleep
3	Criptogenic	N	N/N	N	Right > left bilateral generalized	ESES	Normal	Generalized
4	Criptogenic	N	–	N	Generalized	ESES	Normal	Normal
5	Criptogenic	N	N	N	Right temporal	ESES	ESES	
6	Criptogenic	N	N	N	Generalized from left frontocentrotemporal	ESES	Normal	Left frontocentral, centroparietal
7	Criptogenic	N	Hypoperfusion in left temporal, posterior parietal, and basal ganglia	Disorganized	Generalized	ESES	Normal	Bilateral posterior temporoparietal
8	Idiopathic	Mild left hyppocampal atrophy	–	N	Left centroparietoccipital, right centrotemporal	ESES	Normal	Normal
9	Symptomatic	Cerebellar atrophy	N/N	Disorganized	Normal	ESES	Normal	Generalized
10	Criptogenic	N	–	N	Generalized	ESES	Normal	
11	Symptomatic	N	–	Disorganized	Generalized	ESES	Generalized from right centrotemporal	Activated with sleep
12	Symptomatic	Periventricular leukomalacia, cortical atrophy	Hypoperfusion in left temporoparietal	Disorganized	Left posterior temporoparietal and right temporoparietooccipital	ESES	Bilateral posterior	Bilateral posterior
13	Symptomatic	Arachnoid cyst in right anterior temporal	Hypoperfusion in right frontal	Normal	Right centrotemporal	ESES	ESES	
14	Criptogenic	Normal	Hypoperfusion in right posterior temporal	Disorganized	Left frontal and temporal, right posterior regions	ESES	Normal	Right centroparietal
15	Symptomatic	Normal	–	Disorganized	Right centrotemporal, left frontotemporal, bilateral occipital, multifocal	ESES	ESES	
16	Symptomatic	Normal	–	Disorganized	Right posterior temporoparietooccipital	ESES	Left centrotemporal, right occipital	Activated with sleep
17	Symptomatic	Cerebellar atrophy	Normal	Disorganized	Generalized	ESES	Normal	Multifocal
18	Criptogenic	Normal	–	Normal	Bilateral frontocentral	ESES	Bilateral frontal, bilateral posterior temporoparietooccipital	Activated with sleep
19	Symptomatic	CT: Calcifications, MRI: Right posterior frontoparietal, left parietal polymicrogyria	Normal	Normal	Left parietal and right hemispheric	ESES	ESES	
20	Criptogenic	Normal	–	Normal	Generalized from bilateral frontal	ESES	Normal	Generalized
21	Idiopathic	Mild cortical atrophy	Normal	Normal	Bilateral posterior regions	ESES	Generalized from bilateral posterior regions	Activated with sleep
22	Idiopathic	Normal	–	Normal	Bilateral frontotemporal, frontocentral	ESES	Normal	Left central

patients), lamotrigine (two patients), clonazepam (CZP) (two patients), or primidone (one patient), phenytoin (one patient), either alone or in combination when diagnosis of ESES. Upon diagnosis of ESES, antiepileptic

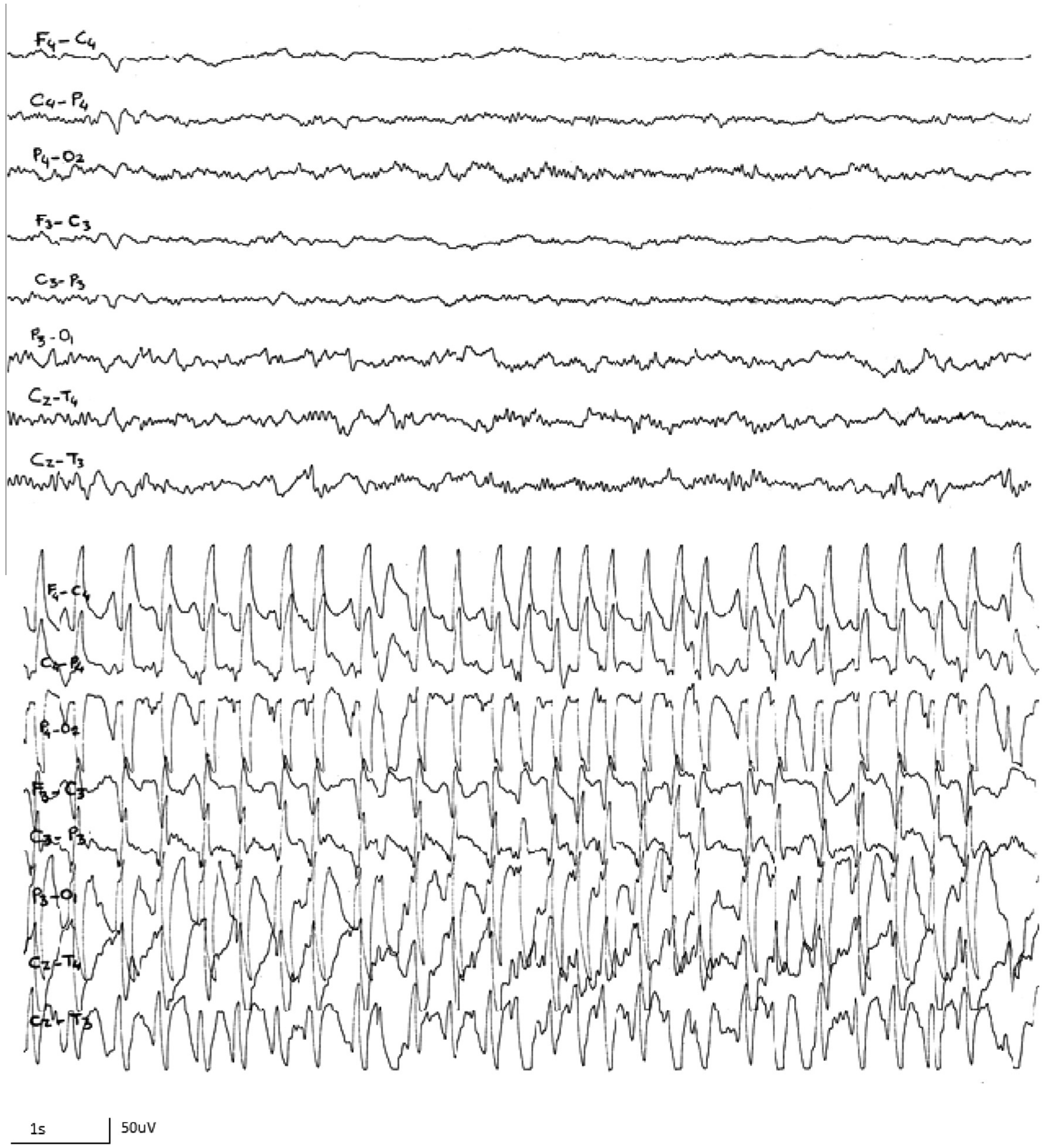

Fig. 1a. EEG recordings of patient 19 show activation of spike-wave activity from wakefulness (top) to NREM sleep (lower).

drugs (carbamazepine, phenobarbital, primidone and phenytoin) that are known to deteriorate ESES pattern were discontinued. Valproic acid was either continued or initiated. Valproic acid was used as monotherapy for an average of 17 months (6 months–3 years) in 13 patients after diagnosis. Although temporary improvement was seen in atonic seizures in two patients (patients 4 and 7), no further effect on ESES pattern was seen. Benzodiazepines such as clobazam (CLB) or CZP, or topiramate (TPM) were started in addition to VPA for second line treatment.

The ESES disappeared following a mean therapy duration of 3.7 months (2–9 months) in 9 of 11 patients (82%) who were started CLB. All patients who had an EEG response showed clinical improvement with decreased atonic and partial seizures. Electrical status epilepticus during sleep disappeared in patient 8 after three months of treatment with CLB, however treatment was discontinued as the drug was not available subsequently and CZP therapy was started due to the re-appearance of ESES on the EEG 14 months later. The ESES had disappeared on the 4th month of CZP treatment.

Clonazepam was used in ten patients and the EEG improved in seven patients (70%) following a mean treatment duration of 6.7 months (2–12 months).

Topiramate was used in eight patients for an average of 12 months (3–24 months) without any improvement in the ESES pattern. Electrical status epilepticus during

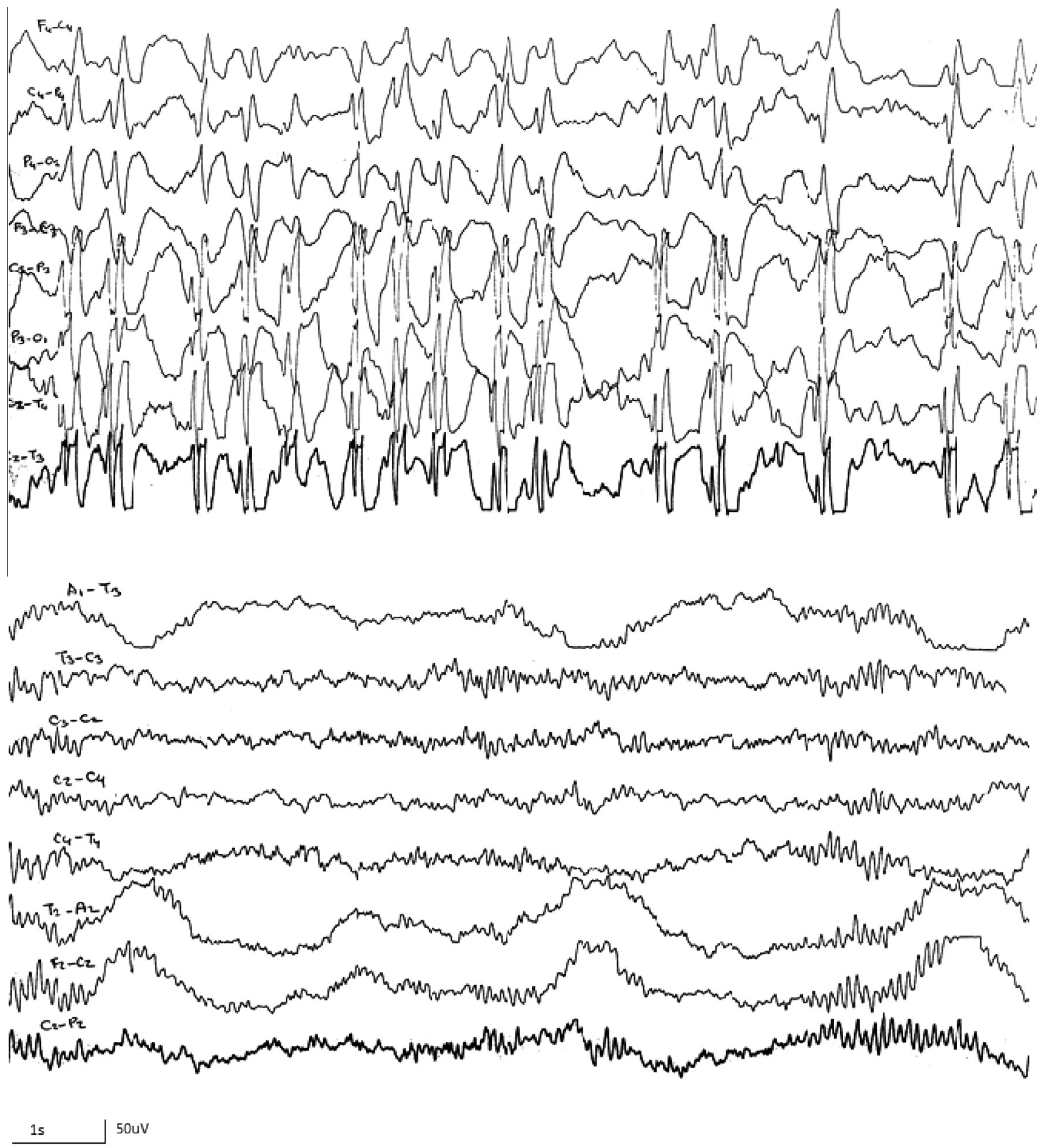

Fig. 1b. Sleep EEG recordings of patient 4 show pre (top) and post (lower) treatment with clonazepam.

sleep improved in only three patients on TPM after the addition of CZP (patient 17), CLB (patient 18) or ethosuximide (patient 20). Topiramate increased atonic seizures markedly in patient 13 and led to a temporary impairment of ambulation.

3.6. Neuropsychological assessment

Neuropsychological test results were available in 21 patients (Table 4). Two consecutive total IQ evaluations were available in 15 patients; 8/15 patients had an initial evaluation at the time of the diagnosis, 7/15 (patients 2, 3, 11, 16 and 18–20) had an evaluation at an average of 2.5 years (1–5 years) after the initiation of ESES. A significant reduction in total IQ values over time was found in 10/15 patients.

Comparison for verbal and performance scores were available in eight patients. These patients showed a significant decrease in verbal scores at follow up ($p < 0.05$) whereas performance scores revealed no difference. The initial IQ scores of 7/19 (37%) patients were normal, but the follow up IQ score was found to be normal only in 2/17 patients (12%).

4. Discussion

Our cases showed a male predominance similar to most previous series [5,11,13–16]. The initial

Fig. 1c. Wakefulness EEG of patient 8 shows epileptiform activity in right centrotemporal (top) and marked generalization of discharges during sleep (lower).

neurological symptom occurred at a mean age of 4.4 years, the diagnosis of ESES was made about three years later. These findings are in accordance with previous studies [4,11,13,14]. Although ESES is known as an age-specific epileptic encephalopathy, persistence of ESES at the second decade has rarely been reported [6,14,17,18]. Electrical status epilepticus during sleep was seen on the EEG in a 17-year-old patient (patient 9) who had seizures during sleep since the age of thirteen. This suggests that ESES may not be specific to age [17].

An etiological factor was identified in 45% of the patients. Eight of the ten symptomatic cases had perinatal insults like perinatal asphyxia, hypoglycemia, or infection. Presence of pre/perinatal insults was reported by Scholtes et al. in 8 out of 10 patients and by Liukkonen et al. in 12 out of 32 patients [6,15]. A significant increase in sleep induced epileptiform activity was reported to be associated with early developmental lesions and thalamic lesions [19]. One of our symptomatic patients had a right anterior temporal arachnoid cyst which could be a coincidental finding. However the presence of convergent EEG findings emanating from the right centrotemporal area may suggest a causal relationship [16,19]. The most commonly reported cortical malformation in the etiology of symptomatic ESES is polymicrogyria. Thirty-eight percent of the patients

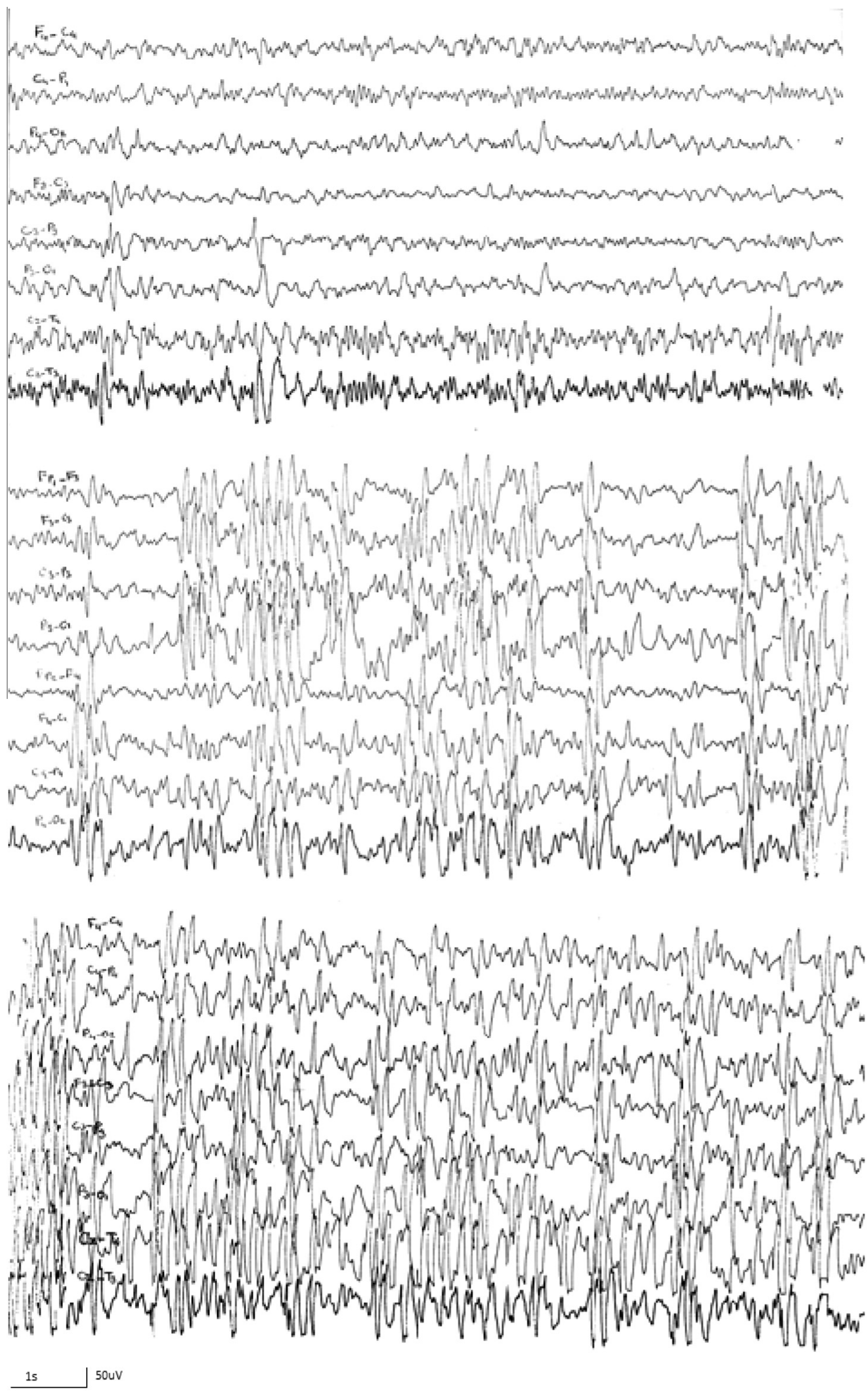

Fig. 1d. Wakefulness EEG of patient 15 shows left centrotemporoparietooccipital epileptiform activity (top) and generalization of discharges during sleep (middle and lower).

were reported to have polymicrogyria in the largest ESES series [11]. It is believed that the preservation of horizontal cortical lamination in polymicrogyria unlike other cortical developmental disorders ensures the rapid spread of the spike-wave discharges [20]. A patient with bilateral polimicrogyria, mental retardation and chorioretinits due to intrauterine cytomegalovirus infection was the sole patient with cortical malformation in our study. Only three patients (13.6) were diagnosed with idiopathic childhood partial epilepsy in the present

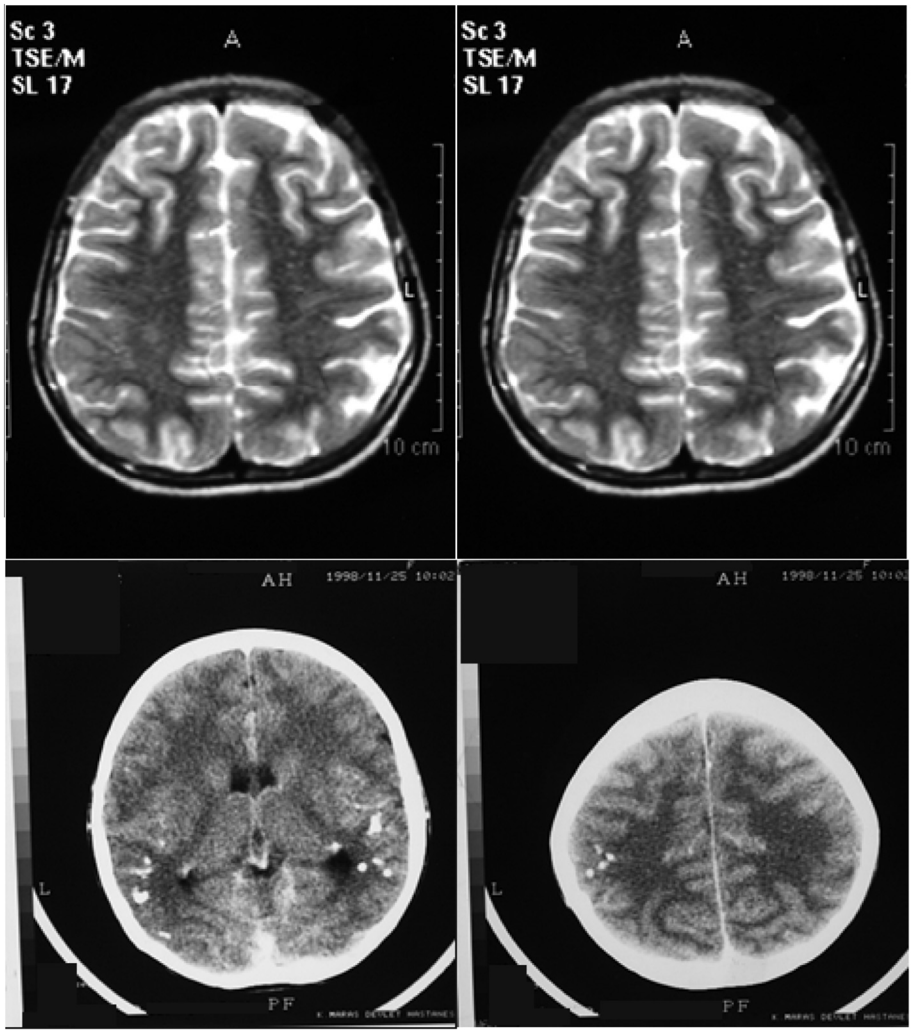

Fig. 2. Axial T2-weighted brain MRI images of patient 19 shows right posterior frontoparietal and left parietal polymicrogyria (top), and computed tomography shows calcifications (lower) related to intrauterine CMV infection.

study yielding a relatively lower proportion compared to the literature with a range between 19% and 37% [11,14,15,21].

The first symptom was seizures in 77% of our patients. The most common seizure types were simple or complex partial seizures in seventeen patients alone or accompanied by other seizure types. The other one-fifth of our ESES patients presented with delayed speech, deterioration in school performance, and behavioral problems such as hyperactivity, restlessness, insomnia, disinhibition, and autistic behavior. Therefore psychological problems were the presenting symptoms in a considerable proportion of the patients. The first symptoms in ESES as reported in the previous studies are also partial motor or generalized seizures in the majority of the patients while 25% of the patients present with other neuropsychological symptoms [3,11,21].

Although lesional-structural cases have an important place in the etiology, nonlesional cases constitute more than half of the patients [4]. Cerebral MRI examination was found to be normal in 64% of our patients. This result is consistent with the opinion that CSWS develops not only due to a macroscopic structural abnormality, but also as a result of a functional disorder of the brain [4].

Single photon emission computed tomography is a functional imaging method used to determine the epileptic focus. Results of SPECT were normal in the active period in all of four patients, excluding the patient with arachnoid cyst. However, focal hypoperfusion was seen in four of the seven patients who underwent SPECT during the remission period. Three of the four patients with hypoperfusion had normal MRIs and one had periventricular leukomalacia without focal cortical lesions. Focal SPECT findings in this study support the presence of a focal epileptic origin that is generalized with secondary bilateral synchrony in ESES [22]. Additionally hypoperfusion on SPECT after cessation of ESES shows persistence of regional dysfunction. Positron emission tomography and SPECT studies have revealed brain

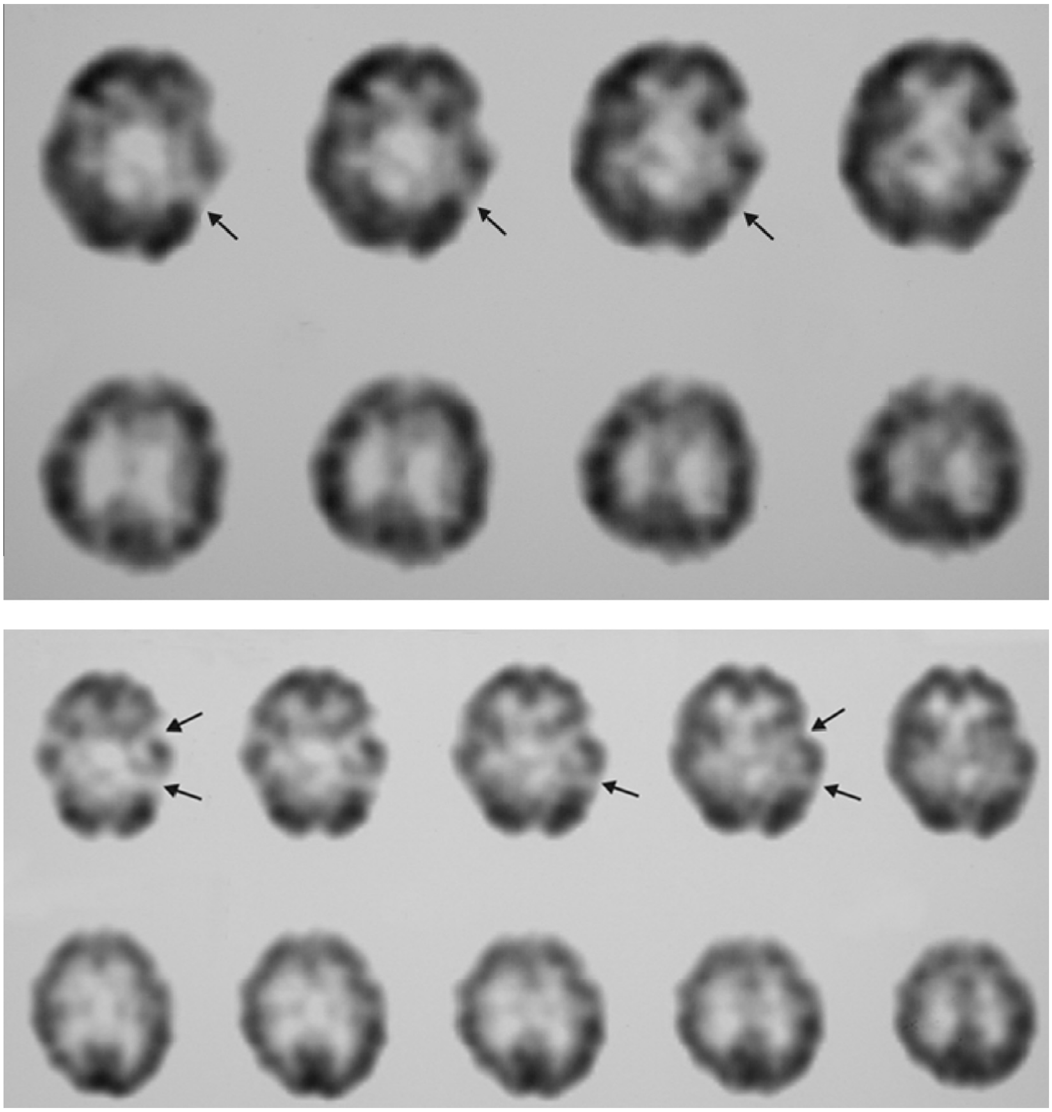

Fig. 3. SPECT of patient 2 shows hypoperfusion in left parietotemporal (top), SPECT of patient 7 shows hypoperfusion in left temporal, posterior parietal, and basal ganglia (lower).

areas of hypermetabolism and hypoperfusion in the perisylvian region and temporoparietal cortex associated with ESES in previous studies [23]. Recent neuroimaging studies on EEG-functional MRI have revealed that, regardless of the etiology, all patients with ESES had activation in the perisylvian regions, anterior cingulate gyrus/prefrontal cortices, and deactivation in task negative network [23]. Therefore, neuropsychological impairment in ESES does not only depend on epileptic focus, but also involvement of related remote brain areas with spike activity [24,25]. These findings might well explain symptoms and signs related to frontal involvement such as hyperactivity, attention deficit, restlessness, insomnia, disinhibition, school failure, and autistic behaviors besides language dysfunction related to temporoparietal cortex involvement seen in children with ESES [23].

The purpose of treatment of ESES is not only elimination of the seizures but also suppressing the interictal activity and to reduce the potential impacts on cognitive functions to a minimum. Benzodiazepines have been chosen in the treatment of ESES since the earliest times [26]. Benzodiazepine drugs alone or in combination with other drugs eliminated ESES in 16 of 21 patients (76%) within a short duration such as 3–6 months in our study. Compared to CZP, CLB eliminated ESES in a greater percentage of patients (70% vs. 82%) and in a shorter time (3.7 months vs. 6.7 months). The reason may be the use of an inefficient CZP doses due to its common side effects such as sleepiness, and the related perception impairment, and ataxia. The good response to these two drugs was within the first 6 months after initiation in 13 of the 16 patients. This shows that the improvement in the EEG does not emerge due to the spontaneous

Table 3
Drug treatment.

Patient	Drug treatment at diagnosis of ESES	Drug treatment after diagnosis of ESES/duration (month/year)	EEG
1	CBZ	VPA + TPM 2 y	ESES: Improvements temporary
2	CBZ + VPA	VPA 6 m	ESES
		VPA + CZP 6 m	ESES improved
3	VPA	VPA 1 y	ESES
		CLB 3 m	ESES improved
4	–	VPA 1 y	ESES
		VPA + CZP 2 m	ESES improved
5	PB	VPA 6 m	ESES
		VPA + CZP 6 m	ESES
6	CBZ, VPA, Primidone	VPA 18 m	ESES
		CLB 3 m	ESES improved
7	CBZ	VPA 2 y	ESES
		VPA + CLB 3 m	ESES improved
8	VPA	VPA + CLB 3 m	ESES improved
		VPA + CZP 4 m	ESES improved
9	VPA	VPA + CLB 2 m	ESES improved
10	VPA + LTG + CZP	VPA + CLB 6 m	ESES
		VPA + CZP 6 m	ESES improved
11	–	VPA 2 y	ESES
		VPA + CLB 9 m	ESES improved
12	VPA + CBZ + Phenytoin	VPA 18 m	
		VPA + TPM 7 m	ESES: improvements temporary
13	VPA	VPA 6 m	ESES
		VPA + TPM 6 m	ESES
14	VPA	VPA + CLB 3 m	ESES improved
15	VPA + PB	VPA + CZP + TPM 18 m	ESES
16	PB	VPA 2 y	ESES
		VPA + CZP 5 m	ESES improved
		VPA + CLB 3 m	ESES improved
17	CZP + PB	VPA 2 y	ESES
		VPA + TPM 2 y	ESES
		VPA + TPM + CZP 1 y	ESES improved
18	VPA + CBZ	TPM 6 m	ESES
		TPM + CLB 5 m	ESES improved
19	VPA	VPA + CZP 7 m	ESES
		VPA + CZP + TPM 2,5 m	ESES
20	LTG	LTG + VPA 1 y	ESES
		LTG + VPA + CLB 6 m	ESES
		LTG + TPM 6 m	ESES
		LTG + TPM + ESM 3 m	ESES improved
21	PB + CBZ	VPA 3 y	ESES
		VPA + CZP 1 y	ESES improved
22	VPA	VPA	–

remission or natural evolution of ESES, but it is a response to treatment [15].

Inutsuka et al. reported that the EEG improved in 47% of their patients with valproate therapy in doses that kept the serum level over 100 μg/ml [27]. However, VPA monotherapy was found ineffective in larger case series [15,21]. Similar inefficient results were observed in our patients too and VPA alone was not effective in improving the ESES. Although VPA is a drug commonly used for effectiveness on various types of seizures seen with ESES, it does not seem to be an option for monotheraphy as it fails to improve ESES.

TPM had been reported to have beneficial results in ESES treatment in the early publications [28]. We administered TPM in eight patients without improvement in EEG and seizure control. Topiramate did not show any efficacy in other studies either [11,21].

Ethosuximide, steroids, intravenous immunoglobulins (IVIg) and ketogenic diet have been recommended for treatment of ESES [21,27,29,30]. We have used antiepileptic medications only, due to effectiveness of IVIg and steroids mostly in LKS patients [27,31]. Ketogenic diet is a relatively new treatment choice for ESES.

The major parameters in the follow-up of ESES are not only the frequency and severity of seizures as in other epilepsies, but also the results of sleep EEGs and serial behavioral and cognitive evaluations regarding potential impacts [32]. A significant decrease in total

Table 4
Neuropsychological testing.

Patient	Follow up	ESES period	IQ_{first}			IQ_{last}		
			Verbal	Performance	Total	Verbal	Performance	Total
1	4 years	2.5 years	84	67	73	72	64	66
2	1.5 years	13 months	53	50	50	52	40	42
3	2 years	15 months	–	–	44	–	–	50
4	2 years	15 months	–	–	109	–	–	–
5	1 years	1 years			80			69
6	5 years	2 years	97	101	99	60	81	67
7	6 years	2 years	Unable to test (autistic)					
8	3 years	2 years	110	91	101	85	76	79
9	7 years	6 months			50			50
10	1 years	1 years			68			
11	5 years	3 years	88	0		60	64	60
12	3 years	2 years			40			40
13	1 years	1 years	97	94	95			
14	2 years	6 months	98	99	98	90	104	96
15	2 years	2 years			70			45
16	4 years	3 years			54	53	57	53
17	10 years	5 years	–	–	0–20	–	–	0–20
18	2 years	1 years	81	92	86	90	92	91
19	10 months	10 months			47			46
20	3.5 years	2 years 3 months						40
21	14 years	4 years	112	76	94	84	68	74
22	4 years	New diagnose	129	113	124			

IQ levels was found in 66% of our patients. Verbal scores were significantly affected, whereas the decrease in performance scores was not significant. The long ESES duration (22.4 months) and the lack of a response with VPA monotherapy for an average of 17 months in the majority of the patients may explain the poor cognitive outcome. The relatively lower rate of patients with idiopathic partial epilepsies known to have an excellent prognosis may also have contributed to the poor prognosis in this study [11]. Comparable results were reported in other studies. Pera et al. found decreased global IQ in 84% of the patients [12]. Caraballo et al. reported intellectual deterioration in 75 of 117 patients [11]. Liukkonen et al. reported that pre-ESES IQ could not be regained in 68% of patients and that there was an unfavorable cognitive outcome [15].

Our study documents patients who were diagnosed with ESES in early 2000s when the knowledge regarding treatment, outcome and functional imaging were emerging. This case series presents patients who were treated with old generation antiepileptic drugs and also those who were started new generation antiepileptic drugs such as CLB and TPM, reflecting a historical perspective with regards to medical treatment of ESES.

Electrical status epilepticus during sleep is an EEG pattern manifested in some rare childhood epileptic encephalopathies. ESES should be considered in children with behavioral, cognitive, and speech problems with or without seizures and these children should be investigated with sleep EEGs. Clinically, it appears with seizures and newly developing neuropsychiatric symptoms. Although EEG shows generalized epileptiform activity during sleep, the high frequency of focal seizures and focal findings on SPECT suggest a focal origin. Clonazepam and CLB are the most favorable treatment options. Valproic acid should not be preferred as monotherapy as it has no effect on EEG. Topiramate does not seem suitable for the treatment of ESES.

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